DIRECTLY OBSERVED TREATMENT SHORT-COURSE (DOTS)

Protocol for Tuberculosis Demonstration Projects in Russia

U.S. Centers for Disease Control and Prevention
and
U.S. Agency for International Development
in collaboration with
Central Tuberculosis Research Institute
Russia Academy of Medical Science
and
World Health Organization

June 1999 (original version)
August 2000 (revised version)

TABLE OF CONTENTS

I. BACKGROUND

The basic tuberculosis (TB) control package, directly observed treatment short-course (DOTS), is the strategy recommended by the World Health Organization for National TB Control Programmes throughout the world. The strategy consists of five elements: 1) Political commitment; 2) Accurate laboratory-based case diagnosis; 3) Directly observed treatment meeting strict bacteriologic and clinical case definitions for the entire course of treatment; 4) An adequate and uninterrupted supply of quality anti-tuberculosis drugs to treat all diagnosed cases; and 5) A mechanism for monitoring program activities to assess service quality and analyze specific treatment outcomes using a standardized recording and reporting system.

DOTS, when properly conducted, can have a profound impact on the tuberculosis problem in the areas of Russia where it is implemented. It will prevent deaths and disabilities among the most productive age groups, and, at the same time, make more effective use of scarce resources by reducing length of hospitalization, number of beds, and other costly interventions. The benefits should be a reduction of tuberculosis prevalence from current levels and a decline in the annual risk of tuberculosis infection. In addition, mortality from tuberculosis should decline within a few years. Eventually, a decline in the annual number of new cases due to reduced transmission of tubercle bacilli in the community will follow. The final effect should be a permanent reduction of incidence rates.

Russian officials, United States Agency for International Development (USAID), Centers for Disease Control and Prevention (CDC), and WHO have agreed to implement projects to demonstrate the effectiveness of DOTS for the general population in three oblasts. These oblasts were selected for the demonstration projects based on a combination of needs and attributes.

Needs include:

- High incidence and prevalence of tuberculosis;
- Failure of current case treatment and management strategies to adequately prevent and control tuberculosis;
- Proclivity for continued transmission and increased incidence of tuberculosis and multidrug-resistant tuberculosis.

Attributes include:

- Priority areas of the Russia CTRI and Ministry of Health;
- Existing tuberculosis infrastructure;
- Local government support and capacity;
- Representative nature of the oblasts and usefulness as demonstration sites.

The projects can have a positive impact on the tuberculosis problem in the selected oblasts, and the strategy of DOTS can later be replicated in other oblasts.

II. GOALS, OBJECTIVES, AND BENEFITS

Goals

1. To reduce the mortality, morbidity, and disease transmission and to prevent the development of drug resistance in the project oblasts in Russia.
2. To strengthen local capacity for on-going tuberculosis control in the future

Objectives

1. To obtain sputum specimens prior to initiating therapy from 100 percent of pulmonary tuberculosis patients for smear, culture, and drug susceptibility results which will be used to guide treatment.
2. To provide directly observed treatment using standardised short-course multi-drug therapy to 100 percent of patients with newly diagnosed and previously treated tuberculosis.
3. To obtain a bacteriologic cure rate of 75 percent or more for new cases confirmed to have pulmonary tuberculosis by bacteriologic methods.
4. To detect 70% of expected cases of bacteriologically positive tuberculosis

Benefits

1. Improved systems of diagnosis and standardisation of treatment of tuberculosis patients will be introduced.
2. Laboratory equipment for diagnosing tuberculosis will be upgraded.
3. A source and maintenance system to ensure regular drug supply will be established.
4. A complete system of patient recording, reporting, monitoring, and follow-up will be initiated.
5. Funds being used for unnecessary x-rays, laboratory examinations, and extensive hospitalisation of tuberculosis patients can be redirected to more cost-effective methods of patient treatment and management.

III. METHODS

A. Technical Aspects of the Projects

In terms of case-finding, a strategic framework for identification of patients presenting spontaneously to health facilities and accurate diagnosis of patients, based on chest radiography and sputum examination for initial screening, will be established. The tools and techniques for diagnosing patients will be made available to supplement the technology and equipment currently used in the tuberculosis reference laboratories.

In terms of treatment, directly observed short-course chemotherapy, the most effective and efficient method of curing tuberculosis patients, will be adopted as the standard of care. Utilising the existing infrastructure, which supports adequate hospital beds and medical staff for in-patient care, the best way to ensure compliance with therapy is to provide the initial phase of treatment in hospital. During the continuation phase, treatment and monitoring of treatment should be provided on an ambulatory basis. Regarding the current situation whereby children with tuberculosis are not allowed to return to school until completing treatment, they may either remain as inpatients for the continuation phase of treatment or come to the hospital as day patients in order to continue their education.

Treatment regimens based on WHO recommendations will be utilised for all cases in three treatment categories. Considering the level of drug resistance in general, a four-drug regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol will be used. Streptomycin will not be used in new cases because of the known high level of resistance to this drug. Patients will be individually registered using standard WHO-recommended registers. Monitoring of treatment will be performed according to WHO standards and through the use of cohort analysis.

Before project implementation, a tuberculosis manual based on the WHO strategy of tuberculosis control will be provided and staff will be trained. The Central Tuberculosis Research Institute (CTRI) will use approved course materials to train the oblast and raion supervisors, co-ordinators, and laboratory staff.

B. Organizational Structure

A Central Unit, an Oblast Unit, and Raion Units will be established to implement, manage, and evaluate the projects. In Orel Oblast, a Prison Unit will also be established and integrated into the project.

1. Central Unit

The CTRI in collaboration with CDC, USAID, and WHO is responsible for overall management of the projects in the demonstration oblasts. A Project Manager for each oblast will be appointed by the CTRI Director. The main functions of the Central Unit are to:

a. Plan the operational steps in implementing, monitoring, and evaluating the DOTS program and its future expansion.

b. Co-ordinate and monitor the projects by quarterly supervisory visits. Feedback will be provided to the Oblast Unit in a written report with findings and recommendations.
c. Train the personnel involved in the projects.
d. Perform quality control of cultures and drug resistance studies.

2. Oblast Unit

The Director of the oblast tuberculosis service, in consultation with the CTRI Project Manager, will appoint a Project Supervisor in each oblast. The functions of the Oblast Unit, based in the tuberculosis dispensary, are to:

a. Work closely with the CTRI in implementing, monitoring, and evaluating the projects.
b. Co-ordinate tuberculosis control in the raions and supervise the personnel involved in case-finding and treatment of tuberculosis. The Supervisor will visit each raion at least once every three months and provide a report with findings and recommendations.
c. Provide reference laboratory services that include culture and drug susceptibility testing of initial specimens, culture of smear-negative specimens collected during treatment, and culture and drug susceptibility testing of smear-positive specimens collected during treatment. The oblast reference laboratory will notify the raion laboratories of results in a timely manner and record culture and drug sensitivity results in the oblast laboratory's database.
d. Organise training programs in raions, in collaboration with CTRI, and provide on-the-job training to health workers.
e. Supervise the maintenance of the written oblast tuberculosis register and ensure that all smear, culture, and drug susceptibility results for each patient are properly recorded.
f. Ensure that quarterly reports on case-finding and results of chemotherapy are made in each raion and sent to the Oblast Unit.
g. Check the quarterly reports for accuracy, enter data into the computer, perform data analyses, and send the reports to CTRI.
h. Acquire and distribute supplies needed in the projects such as anti-tuberculosis drugs (to check whether drugs are ordered, delivered, stored, and distributed to the Oblast and Raion Units),laboratory equipment and supplies, forms, registers, manuals, etc
i. Coordinate anti-tuberculosis activities with general hospitals, clinics, and raion and oblast TB dispensaries and TB clinics (cabinets).
j. Develop a plan for health education to raise community awareness of tuberculosis (See Section III.C.) and appoint a staff member to be responsible for implementation of the plan.
k. Develop and implement a plan for default tracing for the oblast; the ultimate responsibility for default tracing belongs to the project supervisor.

3. Raion Unit

The Director of the oblast tuberculosis service and the Project Supervisor will appoint a Raion Co-ordinator in each raion of the oblast to manage project activities at the raion level. The Co-ordinator will, among other duties, have responsibility for the raion tuberculosis register. A person will be appointed to be responsible for the microscopic examination of sputum and maintain the raion laboratory register. In each raion, one general hospital will be selected as a reference case-finding service, taking into consideration the availability of qualified clinical and microbiological laboratory services and chest x-ray facilities.

The Raion Co-ordinator has the following responsibilities and tasks:

a. Implement the project at the raion level through the tuberculosis and primary healthcare staff.
b. Supervise treatment throughout the raion to ensure that:
    - recommended regimens are prescribed;
    - patients enrolled in the initial phase of short-course chemotherapy are observed to ingest medicines directly by the hospital workers and in the continuation phase are observed to ingest medicines directly by primary health care personnel, other health staff, or other designated health workers;
    - regimens are given for the required period and patients who have completed the prescribed course of short-course chemotherapy are discharged from treatment; and
    - sputum is examined on Ziehl-Neelsen staining for tubercle bacilli and specimens are sent to the oblast reference laboratory for cultures at given intervals. For patients living far from the general hospital or who have difficulties in travelling, the Raion Co-ordinator must instruct feldshers, nurses, or other peripheral health workers on collection of sputum and its transport to the nearest laboratory for follow-up examinations and make sure that this occurs.
c. Assist health workers in the expansion of tuberculosis case-finding in all designated health facilities of the raion.
d. Introduce and supervise the accurate updating of the raion tuberculosis register. Verify that the appropriate initial and treatment monitoring smears and cultures are done and results properly recorded.
e. Monitor the inventory of and process orders for anti-tuberculosis drugs, laboratory reagents, sputum containers and slides, and forms for the raion.
f. Implement the oblast plan for default tracing in the raions.

4. Prison Unit

The Director of the oblast civilian tuberculosis service will appoint a project supervisor to co-ordinate project implementation and activities with the staff of the prison tuberculosis control program and sizo tuberculosis hospital which is under the jurisdiction of the Department of the Implementation of Sentences (DIS) of the Ministry of Justice. The project supervisor will monitor case-finding, diagnosis, laboratory activities, treatment, and case registry for the prison system based on protocol specifications and built upon the existing infrastructure for tuberculosis control. Provision of tuberculosis drugs and other essential resources for implementation of the project in the prison system will be managed and co-ordinated by the supervisor through the civilian tuberculosis service.

C. Health Education

The general public should be taught the importance of early attendance at a health facility if symptoms indicative of suspected TB, especially cough, persist for three weeks or more. Patients with these symptoms should present themselves at the nearest health facility. Early diagnosis and initiation of treatment decreases the transmission of infection in the community which, in turn, helps to improve the health, economic and social conditions of the community.

In addition, efforts should be made to make people aware of the nature of tuberculosis - it is curable with adequate treatment but may result in infection of other people or in disability and death of the individual, if not treated properly. Additionally, curing an individual's disease preserves or quickly restores their capacity to work and maintain their socio-economic position.

Tuberculosis, although completely curable with adequate treatment and largely preventable, is a major cause of death and disability. Therefore, health workers must continually remind the public and policy makers of the importance to fight against this disease. Furthermore, the public should be made aware that the diagnosis and treatment of tuberculosis is free of charge.

IV. LABORATORY SERVICES INVOLVED IN DETECTION, DIAGNOSIS AND CONTROL OF TUBERCULOSIS

Clinical and diagnostic laboratories and inoculation stations based in the general health facilities and district tuberculosis control services, as well as bacteriological, clinical and diagnostic laboratories under tuberculosis control services are involved in detection, diagnosis and control of tuberculosis. All these laboratories perform microscopic examinations of sputum smears stained by the Ziehl-Neelsen method.

An Oblast reference laboratory will be organized under the setting of the bacteriological laboratory of the Oblast TB Dispensary.

A. Clinical and Diagnostic Laboratories and Inoculation Stations in the General Health Facilities and District Tuberculosis Control Services

These laboratories perform smear microscopy examinations and are supervised by the raion reference laboratory. All positive slides and 10 percent of negative slides of patients or, at the laboratory supervisor's discretion, all slides for the reporting period will be sent to the raion reference laboratory once a month for quality control of their examination or reviewed by the supervisor during his/her regular visit. All the laboratories dealing with sputum smear microscopy should maintain a separate laboratory register for TB patients.

The general health facilities, including their own inoculation stations, should provide for smear and culture examinations to be performed by one and the same laboratory using the same sample of diagnostic material which is properly processed and concentrated by centrifuging.

B. Oblast Reference Laboratory

This laboratory:

1. Follows technical procedures according to the standards set by the central laboratory.
2. Supervises the laboratory activities of the raion and prison system (in Orel) laboratories performing sputum smear examinations with visits to each raion laboratory at least every month for the first 6 months, then every three months.
3. Periodically re-trains laboratory technicians.
4. Performs smear and culture examinations and drug susceptibility testing.
5. Maintains the official oblast laboratory register and records results of smear, culture, and drug susceptibility tests.
6. Standardises, prepares, and distributes staining solutions.
7. Performs Mycobacterium culture identification (*M.tuberculosis*, *M.bovis*, atypical mycobacteria) and the testing of drug sensitivity of the agent to first-line drugs (isoniazid, rifampicin, pyrazinamide and ethambutol).
8. Assures quality of the above laboratory examinations by training the laboratory technicians, providing quality control of the performed tests, monitoring proper recording of test findings and reagent quality, and checking the condition of the equipment and adherence to safety rules. The reference laboratory designates a network of laboratory supervisors responsible for quality assurance of the tests carried out by the raion laboratories by visiting them at regular intervals.

As part of proficiency testing, the currently used system which involves the oblast reference laboratory providing sputum samples to the raion laboratory personnel, to which they are blinded regarding smear status, for staining and reading may be continued. Additionally, all slides of tuberculosis patients that are read at the raion and oblasts levels will be kept for quality control. Quality control is based on checking a 10 percent sample of all slides on a quarterly basis. The technicians in the reference laboratory must be blinded as to the original results and the slides from the raion laboratory must be mixed together. The reference laboratory supervisor assesses and evaluates the collection of sputa and the preparation and staining of smears in the raion facilities. Head of the reference laboratory organizes the work of the raion laboratory supervisors and monitors the situation with detection, diagnosis and control of tuberculosis management in the laboratories of every level.

D. Central Reference Laboratory

Functions of the Central Reference Laboratory are assigned to the Laboratory of Microbiological Diagnosis of Tuberculosis of the CTRI (RAMS, Moscow).

This laboratory:

1. Exercises control over establishing, implementing, and supervising the system of quality control for sputum smear microscopy at the raion and oblast levels, for sending feedback of the quality control to the laboratories, and for cultures and drug susceptibility testing at the oblast reference laboratory.
2. Conducts training courses for microscopists, technicians, and other laboratory staff.
3. Makes supervisory visits to the oblast and raion laboratories at least every three months and provide a written report as feedback with findings and recommendations.
4. Performs culture and susceptibility testing for first- and second-line drugs in specific cases, such as failures, and for drug resistance studies.

V. CASE FINDING AND DIAGNOSIS[1]

A. Case Finding

Priority will be given to passive case-finding based on persons with symptoms indicative of tuberculosis spontaneously going to health care facilities. Active case-finding should be limited to examining the household contacts (especially children and young adults) of all patients diagnosed with smear-positive pulmonary tuberculosis and should begin as soon as the diagnosis of tuberculosis (of the index case) is made. Evaluation of contacts should begin with an assessment of symptoms consistent with tuberculosis. Those contacts who are symptomatic should have a chest radiograph performed and undergo sputum smear analysis. Based on this evaluation those diagnosed with tuberculosis should begin treatment under the guidelines of the DOTS protocol promptly. Tuberculin skin testing for asymptomatic children to determine the need for preventive chemotherapy should be administered.

Before the project is implemented, the inhabitants of the demonstration oblasts will be continuously informed of the importance of symptoms for detection of tuberculosis by articles in local newspapers and announcements on radio and television and that the evaluation for and treatment of tuberculosis are free. The Central and Oblast Units will provide mass media with the necessary background material. Persons with symptoms indicative of tuberculosis should be told to present to the nearest available health care facility (feldsher points in villages, polyclinics in towns).

At the local facilities, those who have productive cough that lasts for three weeks or more, frequently accompanied by loss of weight, chest pain, shortness of breath, fever, or hemoptysis, will be referred without delay to the reference general hospital for chest radiograph and bacteriologic evaluation (sputum smear examination on Ziehl-Neelsen staining, cultures).

B. Diagnosis

At the time the patient presents for evaluation, a chest radiograph is obtained. For all patients suspected of having tuberculosis, even those with normal chest radiographs, three separate sputum specimens should be collected for microscopic examination for acid-fast bacilli. If necessary, these sputum specimens will then be sent to the oblast reference laboratory for mycobacterial culture and drug susceptibility testing**.** (See Annex 1 for diagnosis algorithm)

Sputum examination will be done primarily on an ambulatory basis. The first sputum is obtained on the spot under the supervision of a health worker (Day 1). Then the patient is given a sputum container to collect an early morning specimen before his second meeting with the health worker. When the patient returns with his second specimen (Day 2), the third sputum will be collected under the supervision of a medical worker. In selected situations, such as patients living far from the general hospital or with no means of transportation, the patient may be admitted to the

[1] The Protocol includes all activities of primary importance for the DOTS Program which does not exclude a possibility (provided the needed resources are available) of conducting regular national activities on a wider scale.

hospital for two-three days to complete the tuberculosis screening. In some areas it may be necessary to instruct feldshers or other peripheral health workers on collection of sputum and its rapid transportation to the nearest clinical and diagnostic laboratory (CDL) of the participating general health facility. This may be particularly relevant for the follow-up sputum examinations during treatment. Should the first specimen be positive by microscopy and should the patient not return for the second specimen, an immediate search must be made to find the patient to prevent dissemination of infection in the community and deterioration of the patient's condition.

The Raion Co-ordinator will be responsible for ensuring in exceptional circumstances, such as a patient's being unable to reach the hospital, that primary health staff (feldshers, physicians of general health care facilities, etc.) assist with the sputum examination process by collecting patient specimens as described above and then sending them to the participating general hospital laboratory within 24 hours. The location, training, and supervision of these personnel should be planned by staff of the Raion Unit.

The results of smear examination and chest radiography should be evaluated by the physician in the polyclinic/hospital (or phthisiologist (tuberculosis specialist)) without delay by Day 2 after the patient's initial presentation.

The possible clinical scenarios based on the sputum smear, patient's history, and chest radiograph include:

1. A symptomatic patient with no lung abnormalities on chest radiograph and three sputum smears negative for acid fast bacilli is not considered as a tuberculosis case and is treated according to the patient's clinical condition.

2. A symptomatic patient with lung abnormalities on chest radiograph and three sputum smears negative for acid fast bacilli should be evaluated for other aetiologies of lung disease while mycobacterial cultures from the patient's sputum are processed in the laboratory for up to 8 weeks. In the interim, if the patient is thought to have bacterial pneumonia, he or she should be treated with an antibiotic with the needed bacterial spectrum that would cover the likely pathogens for up to 14 days at the nearest general hospital. Rifampicin, streptomycin, and ofloxacin should **NOT** be used in this situation. After completing the prescribed therapy, the patient should be re-evaluated clinically, radiographically, and bacteriologically as described above, including three additional sputum smear analyses and sputum mycobacterial culture. In instances where patients have chest radiograph findings highly suggestive of tuberculosis (cavitations, upper lobe infiltrates, etc) but have three negative sputa, if possible, the patient's evaluation should proceed with further aggressive diagnostic evaluation such as bronchoscopy. The final decision regarding diagnosis will be made at the Oblast TB Dispensary.

3. A symptomatic patient with or without lung abnormalities on chest radiograph and sputum smear positive for acid fast bacilli is referred without delay to the raion or oblast dispensary for admission and treatment. The Raion Co-ordinator must be immediately provided with the necessary information to register the case.

4. An asymptomatic patient with lung abnormalities on chest radiograph should be evaluated further with bronchoscopy and biopsy as necessary. Any specimens from bronchial washings

and/or biopsy should be evaluated with stains for acid fast bacilli and with mycobacterial cultures. If bronchial washings and/or tissue stains are positive for acid fast bacilli, treatment for tuberculosis as outlined in the protocol should be initiated until culture results are available to further determine the treatment course. If washings and/or tissue stains are negative for acid fast bacilli, treatment for TB should not be initiated, but culture results should be followed for 6-8 weeks. If the condition of a patient is serious and his/her life is in danger the treatment can be initiated immediately upon the decision of the Central Medical Commission.

Before a patient with a positive sputum smear has treatment for TB initiated, the patient's sputum should be sent to the oblast laboratory for culture to confirm the diagnosis and for drug susceptibility testing. The same procedure is followed for smear- negative patients, if there are lung abnormalities on chest radiograph**.**

Patients who present directly to a tuberculosis facility should undergo bacteriologic evaluation and receive a chest radiograph according to the same procedures as those patients who present to local health care facilities.

Patients with suspected extra-pulmonary tuberculosis should be referred to the Oblast specialist for confirmation of diagnosis. If the diagnosis of tuberculosis is made, they are registered and started on treatment. The specialists at the oblast tuberculosis dispensary must be consulted about all doubtful cases.

As a rule, the diagnosis of tuberculosis is verified by the Raion Co-ordinator of the raion where the patient lives. If the diagnosis is made in another raion, it is the responsibility of the physician who makes the diagnosis to inform the Raion Co-ordinator of the raion where the patient lives in order to register the patient in the raion of origin.

While useful for screening of suspects, x-ray diagnosis of tuberculosis alone is unreliable, because other chest diseases can resemble tuberculosis on x-ray and pulmonary tuberculosis may show many forms of radiographic abnormality. Consequently, every effort must be made to confirm the diagnosis by bacteriologic evaluation (smear and culture).

Although the diagnosis of tuberculosis in children may not be confirmed by bacteriology and may often require a more sophisticated and comprehensive diagnostic approach (history of contact with infectious TB patients, detailed clinical examination, skin testing, chest radiograph, histology, use of score charts, etc.) children are included in the protocol and will be treated and managed accordingly. They should be reported, registered, and have their treatment analysed according to the procedures established for adults.

VI. TREATMENT OF TUBERCULOSIS

A. Chemotherapy of Tuberculosis

1. Practicalities for administering chemotherapy

Treatment for tuberculosis, including all drugs required, will be provided by the public health care system free of charge to all patients.

All the regimens are short-course and, for new patients, consist of an initial phase of two to three months, as described below and in the tables, followed by a continuation phase of four to six months. For re-treatment cases, the initial phase will be three months followed by a continuation phase of five months. All regimens will be administered under direct observation. During the initial phase, drugs will be administered. During the continuation phase, drugs will be administered daily or intermittently, e.g., Monday, Wednesday, and Friday.

1a. Hospitalisation

Taking advantage of the existing in-patient infrastructure and to ensure compliance with therapy, patients should be hospitalised for the initial phase of treatment. Initial phase treatment is administered under direct observation by a physician or a nurse. The physician or nurse must be present when the patient swallows the drugs.

Hospitalised patients may be discharged after completing the initial phase of treatment. In exceptional circumstances, such as with socially disadvantaged people or with children who cannot legally return to school until treatment is completed, hospitalisation may be extended after the initial phase is completed. New case patients whose smear or culture remains positive after twelve weeks of treatment and relapsed cases whose smear or culture remains positive after sixteen weeks of treatment should be re-evaluated for potential drug-resistant disease.

1b. Discharge Planning

Hospital discharge planning is crucial for uninterrupted treatment in the continuation phase. The head of a hospital department in cooperation with the Oblast supervisor of a corresponding Raion at least at 2 weeks notice before the expected discharge of patients should co-ordinate his actions with the appropriate staff at the Raion (municipal) health facilities and make the patient management plan during outpatient phase. This plan will include specific instructions to the patient about when and where ambulatory treatment will be given. The social needs of the patient, such as assurance of a place to live, transportation from the hospital, and daily meals, should be attended to prior to discharge. Additionally, visits to patients' homes prior to their discharge by available social support staff to further identify obstacles which might interfere with adherence to treatment are useful. Hospital staff should also provide the names and addresses of contacts to the Raion Co-ordinator for comparison with raion records to ensure that all contacts have been identified and examined. (Note: Contact investigation should be initiated by raion health workers as soon as a person becomes a tuberculosis suspect but no later than when the diagnosis of tuberculosis is made). The Raion Co-ordinator should be notified at least one week in advance of the patient's date of discharge, treatment status, prognosis, and other pertinent information.

1c. Ambulatory Treatment

During the continuation phase of treatment of four to six months for new cases and five months for re-treatment cases, treatment will be administered on an ambulatory basis and directly observed by a tuberculosis specialist or primary health care worker (physician, feldsher, or nurse). Direct observation is required to ensure that the patient actually takes all the drugs prescribed. Treatment given on an ambulatory basis requires that a health worker watch the patient swallow the drugs. The health worker and patient must have a mutual understanding of the days, time of day, and place that the drugs will be administered. If the patient will go to an

outpatient treatment center, hospital, feldsher point, or other facility to meet the health worker for drug ingestion, it should be clear to the patient that it is his/her responsibility to keep all appointments. If the patient does not come, the health worker should immediately make contact with the patient by home visit or telephone call and take all necessary measures to ensure that the patient takes the drugs that day or the next day at the latest. The necessity of doing immediate follow-up on any patient who fails to show up at medical facilities to take the drugs cannot be overstated. Prompt and determined outreach by health workers is one of the key factors in establishing and maintaining patient compliance with treatment. Similar steps should be taken with patients who are visited by the health worker at home or other designated location for direct observation of drug ingestion. If the patient is not at the location when the health worker arrives, the health worker should initiate an immediate investigation to find the patient and ensure that the patient takes the drugs that day or the next day at the latest. Family members and respected individuals in the community can be of great help to health workers in their tasks to ensure patient compliance with treatment. It is important for health workers to establish good relationship with family members and take advantage of the assistance of social-community workers and organizations such as the Red Cross.

In both the initial and continuation phases, the patient should take all the drugs at one sitting. Drugs should not be divided into multiple doses given two or three times during the day; all tablets should be taken once daily. The health care worker must verify and record that the patient swallowed the drugs.

2. Drugs

2a. Specific agents for chemotherapy

First-line drugs for treatment of tuberculosis are isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E). Because of documented high levels of resistance to streptomycin (S), E (instead of S) will be used as the fourth drug for treatment of newly diagnosed patients. Fixed-dose combinations of H, R, and Z, and of H and R are available. These combined preparations are recommended because they enhance patient (and health care worker) compliance and afford protection against drug resistance resulting from taking drugs incorrectly. Either the fixed-dose combination or H, R, and Z individually may be used during the initial phase of treatment, since patients' drug ingestion will be supervised in hospital. In the continuation phase, if the fixed-dose combination is used, it must be combined with additional H for use with intermittent treatment regimens to achieve the correct dose of H.

The use of R or S for diseases other than mycobacterial diseases should be limited to very carefully considered indications. Kanamycin, ethionamide, prothionamide, or any other second-line drug must not be used for routine treatment of tuberculosis. Second-line drugs should be reserved and used only to treat patients with drug-resistant disease or patients with a high probability of drug-resistant disease, such as those in whom previous treatment has failed.

2b. Potential adverse effects of agents

In terms of adverse effects of the first-line drugs, H can cause hepatitis but this is an uncommon occurrence and can usually be averted by prompt withdrawal of treatment. In general, serum

transaminase (AST, ALT) levels above five times[2] the upper limit of laboratory normal and/or clinical manifestations of hepatitis is the threshold for which treatment should be withdrawn. More often, a sharp rise in serum concentrations of hepatic transaminases at the outset of treatment is not of clinical significance. If the transaminase levels drop rapidly when dosage is suspended, they are unlikely to rise sharply again when treatment is resumed.

Moderate rises in serum concentrations of bilirubin and transaminases as a result of treatment with R, can be common at the outset of treatment, are often transient and without clinical significance. However, potentially severe dose-related hepatitis can occur, and consequently it is important to not exceed the maximum recommended daily dose of 10mg/kg (600 mg; see annexes 2a and 2b).

Moderate rises in serum transaminase levels are common during the early phases of treatment with Z, but severe hepatotoxicity is rare. Hyperuricemia often occurs during treatment with Z, but this is usually asymptomatic. Gout and arthralgias may also occur.

With E, dose-dependent optic neuritis can readily result in impairment of visual acuity and color vision. Early changes are usually reversible, but blindness can occur if treatment is not discontinued promptly. Therefore, children less than 6 years of age should not receive E due to the inability to more accurately assess vision in young children.

In patients with impaired renal function as indicated by reduced creatinine clearance, dosing with E should be adjusted by increasing the dosing intervals as outlined in Annex 2a and 2b. Pyrazinamide should be avoided in patients with impaired renal function.

3. Patient Registration for Treatment Purposes

It is essential to carefully question the patient about previous anti-tuberculosis treatment before current treatment is started. Cases are, therefore, defined as: new, relapse, treatment after interruption, failure, transferred-in, and "other" case:

- New – A patient who has never had treatment for TB or who has taken anti-tuberculosis drugs for less than four weeks and has never been registered as patient with TB.

- Relapse – A patient who has been declared cured of any form of TB in the past by a physician, after one full course of chemotherapy, or who successfully completed a full course of treatment and has been diagnosed again with TB.

- Treatment after interruption (previously known as treatment after default) – A patient who interrupts treatment for two months or more, and returns to the health service with active TB (as judged on clinical, bacteriological, and radiological assessment).

- Failure – A patient who, while on treatment, remained or became again smear-positive five months or more later after commencing treatment. It is also a patient who was initially smear-negative before starting treatment and became smear-positive after the second month

2 Tuberculosis management in Europe. Recommendations of a Task Force of the European Respiratory Society (ERS), World Health Organization (WHO) and International Union Against Tuberculosis and Lung Diseases (IUATLD) Europe Region. Eur Respir J 1999; 14:978-992.

of treatment or later on. A conclusion regarding failure of treating a patient with extrapulmonary TB is drawn by the relevant specialist in five or more months of treatment.

- Transferred-in – A patient who has arrived from another territory or jurisdiction wherein he was put on a DOTS treatment program to complete treatment.

- "Other" – A patient who was not under the DOTS treatment program but is need of continued treatment and recognized as a promising case for being treated according to the DOTS program.

- Chronic case: A patient who remains sputum smear and/or culture-positive after completing a re-treatment regimen under supervision or a patient who remains sputum smear and/or culture-positive for two years or more.

For registration purposes, patients are assigned to one of three categories based on location and extent of disease and history of previous treatment and sputum smear result:

a. **Category I** consists of new cases of smear- positive pulmonary tuberculosis and other newly diagnosed seriously ill patients with severe forms of tuberculosis, i.e., disseminated tuberculosis, tuberculous meningitis, tuberculosis spondyolitis with neurological complications, tuberculosis pericarditis, peritonitis, bilateral or extensive pleurisy, smear-negative pulmonary tuberculosis with extensive parenchymal involvement, intestinal tuberculosis, genito-urinary tuberculosis, etc.
   With one exception, patients who interrupted treatment will start again on Category I if the length of their treatment before interruption was not more than 1 month.

b. **Category II** consists of relapse and failure patients, those who interrupted treatment, -and "other" patients who were previously treated for more than 1 month not under a DOTS treatment program.
c. **Category III** consists of new cases of smear-negative pulmonary tuberculosis and extra-pulmonary tuberculosis.

For treatment purposes, Category I and III patients will receive the same initial treatment regimen, although the monitoring during treatment will differ between the two. Category II patients will receive a different regimen.

4. Treatment Regimens

No tuberculosis treatment should be started until a firm diagnosis has been made. Empiric treatment trials should be avoided. Sputum specimens should be sent for culture and susceptibility testing prior to initiating treatment.

The following represents the treatments that must be followed for new cases (See Annexes 3a.-c. for treatment algorithms):

4a. Category I -- Sputum smear-positive new cases:

- *Start on treatment with 4 drugs (HRZE)*

- If after 2 months of treatment the patient is documented to be smear-negative, the continuation phase with 2 drugs (HR) is started. The patient's sputum should be re-tested at 5 and 6 months; any patient with a positive smear at 5 or 6 months should be considered a failure, evaluated for drug resistance and started on category II treatment afresh.

- If after 2 months of treatment the patient is still smear-positive, the initial phase should be extended for 1 more month. If the patient is smear-negative after 3 months, the continuation phase with 2 drugs (HR) begins. The patient's sputum should be re-tested at 5 and 7 months; any patient with a positive smear at 5 or more months should be considered a failure, evaluated for drug resistance and started on category II treatment afresh.

- If the patient is instead smear-positive after 3 months AND if initial drug susceptibility tests are available, the following actions should be taken depending on the initial susceptibility results:

    1) If fully sensitive to all drugs (or resistant to streptomycin only): start continuation phase with 2 drugs (HR) and continue for 4 more months. The patient's sputum should be re-tested at 5 and 6 months; any patient with a positive smear at 5 or 6 months should be considered a failure and started on category II treatment afresh.

    2) In case of resistance to one of the four first-line drugs (with or without resistance to streptomycin):

        a) If resistant to ethambutol (+/- streptomycin): start continuation phase with 2 drugs (HR) and continue for 4 more months. The patient's sputum should be re-tested at 5 and 6 months (smear and culture); any patient with a positive smear at 5 or 6 months should be considered a failure and started on category II treatment afresh.
        b) If resistant to INH (+/- streptomycin): start continuation phase with 3 (three) drugs (RZE) and continue for 6 additional months (total 9 months). (If the patient is unable to tolerate pyrazinamide, a 2 drug continuation phase of RE for 9 additional months (12 months total) is also acceptable). The patient's sputum should be re-tested once every other month and at the end of treatment; any patient with a positive smear at 5 or more months of treatment should be considered a failure and started on category II treatment afresh.
        c) If resistant to rifampicin (+/- streptomycin) -- start continuation phase with 3 (three) drugs including isoniazid, pyrazinamide, and ethambutol (HZE) for 15 additional months (18 months total). The patient's sputum should be re-tested monthly thereafter and at the end of treatment; any patient with a subsequent positive smear should be considered a failure and started on category II treatment afresh.

    3) In the case of resistance to two or more of the four first-line drugs (with or without resistance to streptomycin):

a) If resistance to rifampicin and other drugs, or if MDR, perform new culture and susceptibility testing to first- and second-line drugs (3 separate sputum specimens). Category I treatment should be declared a failure for record-keeping purposes in these patients. The Category I treatment regimen should be stopped, and the patient should be started on a DOTS + treatment program, or a second-line drug regimen including at least three drugs to which the patient's tuberculosis is sensitive if DOTS+ is not available.

b) If resistant to 2 or more drugs other than rifampicin, perform new culture and susceptibility testing to first- and second-line drugs (3 separate sputum specimens). Category I treatment should be declared a failure in these patients, and they should be started on the Category II treatment regimen afresh.

4) In patients who are still smear-positive after 3 months but initial drug susceptibility results are NOT available, first- and second-line culture and susceptibility should be obtained immediately on 3 separate sputum specimens, and the drug regimen changed depending on clinical evaluation of the patient.

a) If the patient is doing well clinically and by chest radiograph -- start continuation phase with 3 drugs including HRE. Follow up on all culture and susceptibility results as soon as possible. Based on these results, the above recommendations for continuation therapy (1-3b) should be followed accordingly. Monitor smear, culture, and susceptibility results monthly. If the patient remains smear or culture-positive at 5 months, Category I treatment is declared a failure and the patient is changed to the Category II regimen until the susceptibility results are available. Once the results are available an assessment for the need for changing the patient's regimen can be made.

b) If the patient is not doing well clinically and it can be ascertained that the patient and the provider have adhered strictly to treatment, Category I treatment is declared a failure and the patient is changed to the Category II regimen. Once the initial susceptibility results are available, an assessment for the need to change the patient to a DOTS+ program can be made.

4b. Category II previously treated patients: relapse patients, patients returning after default (smear and/or culture positive), and patients who are failures or potential failures

Category II patients can begin treatment under the protocol once the quality of laboratory susceptibility testing has been proven satisfactory and adequate supplies of capreomycin and ofloxacin are available. Until then, the prevailing category II standard regimen will be used (2 HRZES/ 1 HRZE/ 5 HRE).

- *Send sputum for culture and susceptibility testing, then* start on treatment with 6 drugs (HRZE plus capreomycin and ofloxacin or ethionamide if the patient is a child).

- If the patient has been treated with *ANY* fluoroquinolone previously, then do not use ofloxacin, use ethionamide instead. If the patient has not been treated with a fluoroquinolone previously, then use ofloxacin. (Levofloxacin, ciprofloxacin, sparfloxacin, or grepafloxacin can be substituted for ofloxacin). Culture and susceptibility to first- and second-line drugs testing should be performed immediately on 3 separate sputum specimens.

1) If after 3 (three) months of treatment the patient is smear-negative, continue the initial regimen until the susceptibility results are available. Once the susceptibility results are available -- start the continuation phase as in (1-3b.) under Category I treatment above. If susceptibility results do not become available by 4 months and the patient remains smear-negative, then proceed to the continuation phase and follow the recommendations in 4a-b under category I treatment (above). The continuation phase extends for another 5 months (8 months total).

2) If after 3 (three) months of treatment the patient remains smear-positive, extend the initial phase for 1 more month. If the smear is negative after 4 (four) months -- start the continuation phase and follow the same recommendations (Category I, 1-3b.) regarding the choice of drugs for the continuation phase. Continue these drugs for 5 months (8 months total). Follow the patient with monthly smear, culture, and susceptibility tests. If the patient remains smear and/or culture-positive at 5 months, the Category II treatment should be deemed a failure. The patient should then be changed to a DOTS+ treatment program or to a second-line regimen, including at least 3 drugs to which the patient is sensitive, until the DOTS+ program is implemented.

3) If the patient is still smear-positive after 4 (four) months AND initial drug susceptibility tests are available, treatment should proceed based on susceptibility results as outlined under Category I, 1-3b.

4) If the drug sensitivity results are available at 2 (two) months of treatment and the patient is not doing well clinically and by chest radiograph the treatment should be given according to the recommendations under Category I, 1-3b. depending on the sensitivity findings.

5) If the patient is still smear-positive after 4 months but susceptibility results are NOT available, send sputum (x 3) for culture and susceptibility immediately, and further treatment depends on clinical and radiographic evaluation of the patient:

    a) If the patient is doing well clinically and by chest radiograph, continue the same regimen until the susceptibility results become available. If all cultures are negative, then complete 5 more months of treatment from the time of the first negative culture (presuming no further cultures are positive, minimum 8 months total). If the cultures are positive, continue the same regimen until susceptibility results are available, then follow the recommendations under Category I, 1-3b. If cultures remain positive at 5 months, the treatment is declared a failure and the patient is changed to a second-line regimen including at least three drugs to which the patient's tuberculosis is sensitive until the DOTS+ treatment program is implemented.

    b) If the patient is not doing well clinically and by chest radiograph, treatment is declared a failure and the patient is treated with a DOTS+ treatment program or a second-line regimen including at least three drugs to which the patient's tuberculosis is sensitive until the DOTS+ treatment program is implemented.

4c. Category III -- Sputum smear-negative cases

- Start on treatment with 4 drugs (HRZE)

- If the patient remains sputum smear-negative after 2 (two) months of treatment, the continuation phase with 2 drugs should be started.

- If the patient is found to be smear-positive after 2 months of treatment, the treatment is declared a failure and the patient is changed to the Category II regimen.

NOTES:

1. *It is extremely important to repeat culture and sensitivity at months 2 and 3 in sputum smear-positive patients so that appropriate decisions can be made about their subsequent treatment.*
2. *Patients who are previously treated failure cases should have culture and susceptibility results (x 3) for first-line and second-line drugs obtained, and they should be started on a second-line regimen until the DOTS+ program is implemented.*
3. *Once the treatment is completed, "prophylactic treatment" during spring and fall should not be given for any patients registered to the DOTS project.*
4. *Any deviations from the standardized approach should be decided at the oblast level.*
5. *Regimens using any second-line drugs, including ofloxacin and capreomycin, should be provided only at the oblast level.*

B. Definitions of treatment outcome

Cure

- Patients are considered as cured if his/her smear/culture was positive before the onset of treatment, if they have completed a course of anti-tuberculosis chemotherapy and their smear/culture is negative at 5 or more months of treatment and at the end of treatment [assuming treatment was completed within 9 (nine) months if patient placed on a 6 (six) month regimen, 10 months for a 7 (seven) month regimen, within 12 (twelve) months for an 8 (eight) or 9 (nine) month regimen, or within 21(twenty one) months for an 18 (eighteen) month regimen].

- If the diagnosis was confirmed by culture, there is at least on one occasion a documented conversion (culture-negative) during the continuation phase (with no subsequent positive cultures); or
- If the diagnosis was based on microscopy, there is documented evidence of two negative sputum smears during the continuation phase, one of which must be at 5 months and another one – at the end of treatment.

Treatment completed

- Patients who were smear and culture negative before the onset of treatment and thereafter, and have completed a full course of treatment.
- Patients who were smear and/or culture positive before the onset of treatment and have completed a full course of anti-tuberculosis chemotherapy but failed to have the required number of negative smears and/or cultures.

Treatment failure

- A patient who failed to achieve bacteriologic conversion within *5 (FIVE)* months after the start of treatment, or, after previous conversion, becomes sputum smear or culture-positive again.
- It is also a patient who was initially smear-negative before starting treatment and became smear-positive after completing the initial phase of treatment or later on.
- It is also a patient with tuberculosis resistant to rifampicin plus one of the remaining three main first-line drugs (isoniazid, pyrazinamide, or ethambutol) whom the treating physician decides to refer to a DOTS+ program for treatment.

Death

- A patient who died of any cause during the course of treatment.

Treatment interrupted (default):

Patient whose treatment was interrupted for any reason if:

- Time of interruption was 2 or more months (for those who were treated for more than 2 months – 2 or more weeks) after having received at least 1 month of treatment, or
- The drug intake was less than 80% of the prescribed dose at any given month during treatment, or
- Treatment was not completed within 9 (nine) months if placed on 6 (six) month regimen, 10 months for a 7 month regimen, within 12 months for 8 or 9 month regimen, or within 21 (twenty one) months for an 18 (eighteen) month regimen.[3]

Transfer out

- Patient who has been transferred before the completion of his/her treatment to another jurisdiction or moved to another place of residence and for whom the treatment outcome is not known.[4]

3 Prolonged interruption of treatment, caused by serious adverse effects to the drugs, is also recorded under this heading

4 If result of treatment of the transferred patient is known, then it should be reported in the unit where the patient was initially registered and started treatment.

C. Management of patients who interrupt treatment

The management of patients who interrupt treatment is based on the amount of treatment the patient received before interrupting treatment, the length of the interruption, and, for some patients, the result of a repeated sputum smear examination. Algorithms representing the different scenarios are listed in Annex 5.a.-c.

1. New smear positive patients (category I) who interrupt treatment

1a. Less than 1 month of treatment before interruption

For a patient who received less than 1 month of treatment before interruption and the length of interruption was less than 2 weeks, the patient continues treatment on the category I regimen. The patient must complete all 60 doses of the initial intensive phase before starting the continuation phase of treatment. For a patient who interrupts for 2-7 weeks, the patient restarts treatment on the category I regimen from the beginning. For a patient who interrupts treatment for 8 weeks or more, the patient must have a repeat sputum examination performed. If the patient has a positive sputum smear, the patient's outcome is designated as default, and the patient is re-registered as a category I patient and restarts the regimen from the beginning. If the patient's repeat sputum smear examination is negative, the patient continues the category I regimen to complete all 60 doses of the initial intensive phase of therapy before starting the continuation phase.

1b. 1-2 months of treatment before interruption

For a patient who received 1-2 months of therapy before interruption and interrupted for less than 2 weeks, the patient continues the category I regimen. The patient must complete all 60 doses of the initial intensive phase before starting the continuation phase of treatment. For a patient who interrupts for 2-7 weeks, the patient must have a repeat sputum examination performed. If the patient has a positive sputum smear, the patient should receive 1 extra month of intensive phase treatment of the category I regimen before starting the continuation phase. If the patient's repeat sputum smear examination is negative, the patient continues the category I regimen to complete all 60 doses of the initial intensive phase of therapy before starting the continuation phase. For a patient who interrupts treatment for 8 weeks or more, the patient must have a repeat sputum examination performed. If the patient has a positive sputum smear, the patient's outcome is designated as default, and the patient is re-registered as treatment after default and is started on the category II regimen from the beginning. If the patient's repeat sputum smear examination is negative, the patient continues the category I regimen to complete all 60 doses of the initial intensive phase of therapy before starting the continuation phase.

1c. More than 2 months of treatment before interruption

For a patient who received more than 2 months of treatment before interruption and the length of interruption was less than 2 weeks, the patient continues treatment on the category I regimen. For a patient who interrupts for 2 weeks or more, the patient must have a repeat sputum examination performed. If the patient has a positive sputum smear, the patient's outcome should be designated as default, the patient should be re-registered as treatment after interruption, and the patient should start treatment with the category II regimen from the beginning. If the patient's repeat sputum smear examination is negative, the patient continues the category I regimen; all 60 doses of the initial intensive phase of therapy must be completed before starting the continuation phase.

2. Smear positive patients under re-treatment (category II) who interrupt treatment

2a. Less than 1 month of treatment before interruption

For a patient who received less than 1 month of treatment before interruption and the length of interruption is less than 2 weeks, the patient continues treatment on the category II regimen. The patient must complete all 90 doses of the initial intensive phase before starting the continuation phase of treatment. For a patient who interrupts for 2-7 weeks, the patient is re-registered as other and restarts treatment on the category II regimen from the beginning. For a patient who interrupts treatment for 8 weeks or more, the patient must have a repeat sputum examination performed. If the patient has a positive sputum smear, the patient's outcome is designated as default, and the patient is re-registered as treatment after default and restarts the regimen from the beginning. If the patient's repeat sputum smear examination is negative, the patient continues the category II regimen to complete all 90 doses of the initial intensive phase of therapy before starting the continuation phase.

2b. 1-2 months of treatment before interruption

For a patient who received 1-2 months of therapy before interruption and interrupts for less than 2 weeks, the patient continues the category II regimen. The patient must complete all 90 doses of the initial intensive phase before starting the continuation phase of treatment. For a patient who interrupts for 2-7 weeks, the patient must have a repeat sputum examination performed. If the patient's sputum smear examination is positive, the patient should receive 1 extra month of intensive phase treatment of the category II regimen before starting the continuation phase. If the patient's repeat sputum smear examination is negative, the patient is re-registered as other and continues the category II regimen to complete all 90 doses of the initial intensive phase of therapy before starting the continuation phase. For a patient who interrupts treatment for 8 weeks or more, the patient must have a repeat sputum examination performed. If the patient's smear examination is positive, the patient's outcome is designated as default, the patient is re-registered as treatment after default and is started on the category II regimen from the beginning. If the patient's repeat sputum smear examination is negative, the patient continues the category II regimen to complete all 90 doses of the initial intensive phase of therapy before starting the continuation phase.

2c. More than 2 months of treatment before interruption

For a patient who received more than 2 months of treatment before interruption and the length of interruption was less than 2 weeks, the patient continues treatment on the category II regimen. The patient must have completed all 90 doses of the initial intensive phase before starting the continuation phase of treatment. For a patient who interrupts for 2 weeks or more, the patient must have a repeat sputum examination performed. If the patient has a positive sputum smear, the patient's outcome should be designated as default, the patient should be re-registered as treatment after interruption, and the patients should start treatment with the category II regimen from the beginning. If the patient's repeat sputum smear examination is negative, the patient continues the category II regimen; all 90 doses of the initial intensive phase of therapy must have been completed before starting the continuation phase.

3. Smear-negative patients who interrupt treatment

3a. Less than 1 month of treatment before interruption

For a patient who received less than 1 month of treatment before interrupting treatment and the length of interruption is less than 2 months, the patient should resume treatment and complete all doses. For a patient who interrupts treatment for 2 months or more, the patient should have a repeat sputum examination performed. If the patient has a positive sputum smear examination, the patient's outcome should be designated as default, the patient should be re-registered as new, and the patients should start treatment with the category I regimen from the beginning. If the patient has a negative sputum smear examination, the patient should resume treatment and complete all doses.

3b. More than 1 month of treatment before interruption

For a patient who received more than 1 month of treatment before interrupting treatment and the length of interruption is less than 2 months, the patient resumes treatment to complete all doses. For a patient who interrupts treatment for 2 months or more, the patient should have a repeat sputum smear examination performed. If the patient has a positive sputum smear examination, the patient's outcome should be designated as default, the patient should be re-registered as treatment after default, and the patient should start treatment with the category II regimen from the beginning. If the patient has a negative sputum smear examination, the patient should resume treatment and complete all doses.

D. Pediatric Tuberculosis

The basic principles of treatment of TB in children are essentially the same as in adults. As TB in children is usually an immediate complication of primary infection, they typically demonstrate closed caseous lesions with relatively few mycobacteria. As the probability of acquiring drug resistance is proportional to the size of the bacillary population, children are considered to be at lower risk of developing acquired drug resistance during treatment. The risk of developing extrapulmonary TB, especially disseminated disease and meningitis (requiring prompt and effective treatment), is greater than in adults. Normally, due to pharmacokinetics, children tolerate larger doses of drugs per kg body weight and are less likely to develop side-effects than adults. However, children with disseminated disease and meningitis or those who are malnourished may develop hepatotoxicity, especially when the daily dosage of isoniazid exceeds 10 mg/kg body weight. Owing to the lack of specific drug formulations, the administration of drugs in pediatric subjects may sometimes necessitate the crushing of pills or making non-standardized suspensions. If these problems are not considered in advance, they may cause delays and interruptions of treatment and/or administration of inappropriate doses.

The regimen for pulmonary TB is a 6-month regimen including isoniazid, rifampin, and pyrazinamide during the intensive phase (first 2 months) and isoniazid and rifampin during the continuation phase (4 months). The same regimen is recommended for extrapulmonary TB. It is recommended to continue management of tuberculous meningitis, disseminated TB and pulmonary TB with extensive parenchymal involvement for 9-12 months with the use of four first-line drugs in the intensive phase.

This standard regimen is generally well tolerated. Supplementation with pyridoxine is recommended in malnourished children. Although transiently elevated liver transaminase levels

are described in 3-10% of the children taking isoniazid, the risk of developing hepatotoxicity is very low. Rifampin is well tolerated and adverse reactions such as leukopenia, thrombocytopenia and flu-like syndrome are rare. Pyrazinamide, extensively used in children over the past 10 years, has proved to be well tolerated at a daily dose of 30-40 mg/kg body weight. Streptomycin, less frequently prescribed than in the past, is also well tolerated. The general use of ethambutol in children under 6 years of age is not recommended in existing guidelines because of the difficulties in monitoring optic toxicity, being limited to schoolchildren and adolescents and when drug resistant TB is suspected.

Several second-line drugs, including ethionamide, polypeptides (capreomycin) and aminoglycosides (kanamycin, amikacin) are well tolerated. It is recommended that liver function is tested before the commencement of therapy and, in cases in which the patient is unconscious or uncooperative, every 2 weeks for the first 2 months. Liver function monitoring is mandatory when clinical signs and symptoms (fever, malaise, vomiting, jaundice, and weight loss) appear.

E. Tuberculosis Treatment during Pregnancy and Breastfeeding

Pregnant women with tuberculosis must be given adequate therapy as soon as tuberculosis is diagnosed. The preferred initial treatment regimen is isoniazid, rifampicin, and ethambutol. Streptomycin should not be used because it has been shown to have harmful effects on the foetus. In addition, pyrazinamide should not be used routinely because its effects on the foetus are unknown. Because the six-month treatment regimen cannot be used, a minimum of nine months of therapy should be given. Susceptibility testing is especially important in these circumstances. If the bacilli are fully susceptible, the patient can be treated with isoniazid and rifampicin for nine months. Ethambutol carries with it the risk of optic (and other) neuritis, creating a potential hazard to the eyesight of the developing fetus. If the isolate is resistant to isoniazid or rifampicin, nine months of therapy with an isoniazid/rifampicin regimen are inadequate.

Treatment must be individualised or postponed until after delivery, depending on the stage of gestation and the pattern of resistance.

The small concentrations of tuberculosis drugs in breast milk do not have a toxic effect on nursing new-borns, and breastfeeding should not be discouraged for women undergoing anti-tuberculosis therapy. Similarly, drugs in breast milk should not be considered effective treatment for disease or infection in a nursing infant. Infant children of mothers with tuberculosis should be given chemoprophylaxis for as long as the mother remains infectious and then should be vaccinated with BCG, if still tuberculin negative.

F. Surgical treatment

Surgery is usually not a first line option in the treatment of TB because in most cases pulmonary TB is curable using modern drug regimens. In joint consultation with medical and surgical experts, surgery can and should be considered an adjunct to chemotherapy when all of the following criteria are met:

- adequate first and second line regimens of anti-TB medications have failed to cure

the patient as in the case of multi-drug resistant TB

- the disease is sufficiently localized to allow lobectomy or pneumonectomy
- the remaining lung tissue is relatively free of disease
- the patient has an acceptable surgical risk, with sufficient pulmonary reserve to tolerate the resection
- if possible, smear positive patients should have converted to smear negative prior to surgery

Indications for surgical intervention in TB treatment are:

- Vital indications
  - Severe hemoptysis
  - Tension pneumothorax
- Absolute indications
  - Progressing caseous pneumonia
  - Tuberculoma (>2cm)
  - Round solid coin lesion if doubt of diagnosis
  - Fibrocavernous TB
  - Chronic tuberculous pleural empyema
- Relative indications
  - Large residual post TB changes

In cases where surgical intervention is indicated for patients registered under the DOTS project and still undergoing treatment, the full course of chemotherapy as initially prescribed should be completed as outlined in the protocol with direct observation of the administration of every remaining dose to the patient. If necessary, the duration of treatment can be extended upon the decision of the Coordination Council.

G. Complications of Tuberculosis

1. Pulmonary tuberculosis

a. Hemoptysis (coughing up blood): A patient who coughs up the amount of a small cup or more of blood (severe case) should be prescribed rest and anti-tussives.

b. Spontaneous pneumothorax: A patient whose lung has collapsed through damage caused by tuberculosis may require surgical intervention. The decision depends on the magnitude of the pneumothorax and should be made only after a thorough assessment of the patient's condition has been completed.

c. Pleural effusion: If the amount of fluid is not excessive, the clinical condition will improve with chemotherapy alone. If there is too much fluid in the thorax, drainage may be necessary to relieve symptoms and reduce long term sequelae. Additionally, corticosteroid therapy as an adjunct to the standard tuberculosis chemotherapy may prevent later complications of disease.

d. Cardio-pulmonary insufficiency: A patient with heart or lung disease resulting in cardiac or respiratory compromise may need specific treatment.

2. Extra-pulmonary tuberculosis

Complications depend on the organs involved. A specialist from the oblast dispensary should review all cases with serious complications. For nearly all cases of extra-pulmonary tuberculosis the same chemotherapy should be used as for pulmonary tuberculosis.

a. Spinal tuberculosis: Skilled surgery may be necessary early in the course of treatment of more severe forms of spinal tuberculosis to reduce deformity later.

b. Patients with bone/joint tuberculosis should receive a longer course of therapy (9-12 months)

c. Patients with tuberculous meningitis should receive a minimum of 9-12 months of therapy. Adjunctive corticosteroid therapy may help decrease neurologic sequelae.

H. Diagnosis and Treatment of Tuberculosis Patients Infected with Human Immunodeficiency Virus (HIV)

HIV-related immunosuppression reduces the inflammatory reaction and cavitation of pulmonary lesions, and therefore HIV-infected patients with pulmonary TB can have atypical findings or normal chest radiographs. Therefore, HIV-infected patients who have normal or atypical chest radiographs but for whom the index of suspicion of having TB is high, procedures such as bronchoscopies and bronchoalveolar lavage, biopsies and aspirates (e.g., of lymph nodes or bone marrow), culturing of nonrespiratory clinical specimens (e.g., blood, urine, pleural fluid), and radiologic evaluations other than chest radiographs (e.g., computerized tomographies) should be considered.

HIV-seropositive tuberculosis patients should be treated according to the regimens outlined for category I, II, and III patients. However, the final decision on the length of therapy for HIV-seropositive patients depends on the patient's clinical and bacteriologic response to treatment. In patients with a delayed response, treatment should be prolonged to 9 months. A delayed response is defined as the failure of cultures to convert to negative or symptoms to resolve after 2 months of appropriate tuberculosis treatment.

I. Preventive Chemotherapy

1. Children contacts of smear-positive cases

Asymptomatic children who are contacts of smear-positive cases but are not diagnosed as having active tuberculosis should be evaluated for preventive chemotherapy. For these contacts, a tuberculin skin test should be administered. Infected children should receive a 6 month directly observed course of isoniazid (5mg/kg daily). Children with induration less than 5 mm should receive a 12 week directly observed course of isoniazid and then have a repeat tuberculin skin test performed. If the repeat skin test is positive at 5 mm or greater, directly observed therapy with isoniazid (5mg/kg) should be continued for an additional 12 weeks. If the reaction remains negative (less than 5 mm), therapy need not be continued unless there is continuing exposure to an infectious source case.

2. Persons with human immunodeficiency virus (HIV)

As soon as possible after HIV infection is diagnosed, all persons should receive a tuberculin skin

test (TST) unless previously tested and found to be TST-positive. As soon as possible after learning of an exposure to a patient with infectious TB, all HIV-infected persons should be evaluated for active TB and receive a TST, regardless of any previous TST. TSTs should be conducted periodically for HIV-infected persons who are TST-negative on initial evaluation and who belong to populations with a substantial risk of exposure to M. tuberculosis (e.g., residents of prisons, jails, or homeless shelters).

Candidates for TB preventive therapy among HIV-infected persons who have been determined to not have active TB include:

- Children with a TST reaction size of 5 mm or greater who have not previously received treatment for M. tuberculosis infection should receive TB preventive treatment, regardless of their age.
- Persons who have had recent contact with an infectious TB patient should receive TB preventive treatment, regardless of their age, results of TSTs, or history of previous TB preventive treatment.
- Persons with a history of prior untreated or inadequately treated past TB that healed and no history of adequate treatment for TB should receive TB preventive treatment, regardless of their age or results of TSTs.

Preventive therapy options for patients include:

- A 9-month regimen of isoniazid (5 mg/kg, maximum dose 300 mg, daily or 15 mg/kg, maximum dose 900 mg, twice weekly) administered as directly observed therapy
- A 2-month regimen of rifampin (10 mg/kg, maximum dose 600 mg, daily) and pyrazinamide (25 mg/kg, maximum dose 600 mg, daily) administered as directly observed therapy

VII. CASE MANAGEMENT

A. Background

Case management has become a critical component of effective TB control. The first goal of case management is to insure that each patient with active TB is treated as effectively as possible in order to cure the patient as quickly as possible. The second goal is to find and prevent new cases of TB by evaluating close contacts of the patient, especially if the patient is a child. From these two, the public health goals of minimizing the spread of infection and preventing drug resistance follow naturally.

The case manager typically is an experienced nurse, social worker, or public health specialist. The case manager works closely with the responsible physician to coordinate the "nuts and bolts" of treatment, while the physician remains responsible for the medical decisions regarding treatment. The case manager insures that the physician is fully informed and that correct medical decisions are implemented. At the same time, the case manager insures that the patient is receiving their treatment and the supporting services that will enable the patient to complete treatment in a timely manner.

Case management is necessary for several reasons:

1. Most people will not take all of their medicine exactly as prescribed, especially when the course of treatment is prolonged and the medicines may have unpleasant side effects.

2. Despite best efforts and intentions, physicians cannot reliably predict who will take their medicine correctly. As has been shown in studies previously, adherence to medication is not related to income, education, social standing, occupation, intelligence, age, gender, etc. It is clear, however, that certain segments of the population are less likely to adhere to their treatment regimen, including children, adolescents, alcoholics, other drug abusers, and persons with mental illness or disability.

3. TB carries with it the public health imperative of potential (in fact, highly probably) harm to others in the community if the patient is not compliant with treatment and remains infectious.

4. Since one cannot reliably predict which patients will not take their medicine as prescribed, it becomes the responsibility of the TB control program to insure that they do. The only way to insure that patients take all of their medications correctly is with directly observed therapy (DOT), which is direct administration of the drugs to the patient by a health care worker or another responsible individual who is accountable to the health care system.

At its core, case management means that a designated individual within the health care system is responsible and accountable for making sure that a patient completes their TB treatment. This individual should **do whatever is necessary** to make sure the patient takes his or her treatment. The case manager must know the community and the services that are available to the patient that may facilitate his or her treatment. This is where the concept of "management" is rooted. In addition to monitoring the patient's care, the case manager coordinates the patient's overall care, actively assisting the patient to access medical and social services, and troubleshooting potential barriers to care, and using incentives and enablers to help the patient complete their treatment. Examples might include transportation, food supplements, reporting adverse drug reactions to the physician, initiating and supervising the delivery of treatment at home or in the community, tracing the patient in case of treatment interruption, access to or support for temporary housing for homeless individuals, alcohol treatment or rehabilitation services, and vocational retraining for unemployed individuals.

Effective case management requires administrative commitment and support, including establishing the program policies and procedures, education and training of both staff and patients, and adequate funding.

B. Case management process and implementation

B1. Assign a case manager

The director of the oblast TB services or his or her designee should identify a specific person in the TB control program staff who will be responsible and accountable for insuring that each patient completes the full course of treatment. Although specific duties may be assigned or referred to designated individuals, the case manager is ultimately responsible for insuring that all activities are performed and appropriate outcomes achieved. In general, the case manager is a skilled nurse or social worker whose only job is case management. Typically, the case manager is not the physician responsible for the patient's medical care, because that physician has too many other responsibilities and demands on his or her time. The case manager, however, answers to the physician in charge. Each case manager can manage many cases; the actual number depending on how much time each patient requires.

B2. Inpatient phase – prevention of treatment interruption

a. Patient Education. Few patients understand the nature of tuberculosis, its cause, its cure, and the nature of how it is contagious. Patients must also understand what is required of **them** to complete treatment and the consequences of interrupting their treatment. The HCWs must spend time with patients explaining TB, answering questions, eliciting and allaying concerns, assessing patients' level of understanding, and planning subsequent steps based on this assessment. This individual or small group contact creates within the patient the sense of the importance we as health care providers attach to their illness and its treatment. However, verbal explanations and interactions are seldom enough to give patients a firm, lasting understanding.

1) Develop curriculum, plan and materials for education of patients appropriate to both higher and lower levels of native intelligence and education;
2) Educate patients about the disease and its treatment in general;
3) Educate patient about their specific treatment plan;
4) Use multiple modalities: verbal explanations; written materials (brochures, comic books, booklets, story books); video tapes; posters and other visual aids
5) Repetition, repetition, repetition
6) Assess patient understanding and respond with appropriate educational strategies within the curriculum

b. Social History. Obtain a detailed social history on patient in order to identify consistent routines in the patient's life, whether and how the patient will be able to come to clinic, what enablers and incentives will help the patient come to clinic daily, and where/how the patient can be found if they do not come to clinic -- especially important to include alternative locations and means of contacting the patient. Who does the patient spend time with? To whom does the patient turn for help?

1) Home and work addresses;
2) Family: names, relations, home/work addresses, nature of relationship, frequency of interactions, whether they're close or distant, how often and where they see each other, etc.
3) Coworkers and friends (same details as appropriate)
4) Daily / weekly / monthly routines
5) Social interactions, "hang outs," pastimes
6) Substance abuse - alcohol, drugs
7) Prior imprisonment

8) Homelessness - 2 kinds:
   a) temporary quarters or impermanent housing with relatives, friends, a rented room, a boarding house: get details of where / when;
   b) true homelessness (sleeping in public places, no place to keep your belongings): get details of where / when;

c. Discharge planning. Coordinate transition between inpatient and outpatient care. This is a central function of the case manager whose primary responsibility this is. She or he must meet the patient in the hospital and assure a seamless transition to outpatient care.
   1) Determine what care and services the patient will need and what additional services may facilitate treatment (alcohol rehab, transportation, community-based DOT at home or work, additional medical and social needs);
   2) Identify the providers and the location of these services;
   3) Inform / educate patient on the necessary treatment and the available optional services (from C.1. and C.2. above), where to go and when, and what is expected of him/her to complete treatment. Coordinate the care plan with the patient, and adapt it to the patient's life outside the hospital.
   4) Discuss incentives and enablers with patient and offer them as appropriate to enable the patient to commit to the care plan;
   5) Plan for transportation of patient or outreach to deliver community-based DOT;

d. Prevent patient interruption and defaulting. Periodic psychosocial assessment of patient. Ask patient if they've had thoughts about leaving the hospital. Discuss frankly with them what it would take to keep them in the hospital until MDs discharge them. "Contract" with patients to inform nurse in advance if they want to leave so that nurse / doctor can take appropriate measures to facilitate their continued hospital stay, insure that they return, or arrange for outpatient care and follow-up.

B3. Outpatient phase

a. Monitor Treatment
   1) Monitor adherence with medical follow-up
   2) Monitor clinical, bacteriological, radiological improvement -- report any deterioration to MD responsible for patient (same or next working day)
   3) Monitor adverse effects of medications -- report to MD
   4) Insure appropriate use / delivery of incentives and enablers

b. Continue patient-specific education
c. Coordinate medical care and services

d. Troubleshoot potential barriers to continuity of care
   1) Review / update social history
   2) Identify potential barriers to continuing care
   3) Devise and agree upon solutions with patients

B4. Management of treatment interruption

a. Develop an active system to identify immediately patients who interrupt treatment;

b. Initiate immediate action to return patients to treatment
   1) Phone (if available) and letter -- same day
   2) Home visit -- day following missed medication and each day as needed
   3) Visit relatives, neighbors, friends, work place / coworkers, other locations per social history
   4) Contact hospitals, jails
   5) If patient in another raion or oblast, notify appropriate TB authorities

c. Provide patient with enablers and incentives: transportation, food, social services, housing, etc.

d. Provide training for staff on locating lost patient

e. Establish incentives for case management team
   1) Provide teams with enablers and incentives: proper equipment and supplies, good working environment, transportation vouchers, etc.
   2) Give rewards for successful outcomes

VIII. PROGRAM MANAGEMENT

A. Supervision

Supervisory visits to the Oblast Unit should be made every three months by staff of the Central Unit, jointly with CDC and WHO project consultants. Supervisory visits to each Raion Unit should be made at least once every quarter by the oblast Project Supervisor and other staff as appropriate. In both cases, feedback from the visits in the form of a written report should be provided with findings and recommendations. During these visits, cases diagnosed and started on treatment during the cohort analysis period should be discussed and their records, including laboratory test results and Tuberculosis Treatment Cards, should be reviewed. A plan of action should be developed to address any treatment or compliance problems that are uncovered. Issues related to project operations, such as drug inventory and supply and the work of the laboratories, should also be discussed and plans developed to resolve problems. Work performance and productivity of personnel should be assessed with attention given to supporting and enabling staff involved in the DOTS project to perform at the highest possible level.

The Raion Co-ordinator should make regular supervisory visits to health facilities (general hospitals, dispensary, and clinics) in the raion which are involved in the DOTS project at least every month. On these occasions, the Co-ordinator should assess the anti-tuberculosis activities performed in the different health facilities in order to ensure accurate diagnosis, treatment, monitoring, drug supply, etc. At least every two months the Raion Co-ordinator should also evaluate the work of all the primary health workers treating patients during the continuation phase and provide them with drugs sufficient for one to two months of treatment. A review of patients' medical records and discussions with the primary health workers as well as discussions with some patients and their families are important aspects of these assessments. The planned supervisory visits are an important opportunity to give on-the-job training to primary health workers. If needed, the Raion Co-ordinator can organize local re-training courses for peripheral health staff on case-finding, sputum collection, treatment, treatment monitoring, side effects of drugs, and default tracing, and for laboratory staff on staining and reading of slides, treatment monitoring, etc.

B. Drugs and Diagnostic Material Supply

Providing the regular supply of drugs and diagnostic materials will be the responsibility of the Oblast Unit. This supply should be based on previous case notification data. Stocks should cover up to three months at every raion. The Oblast Unit is responsible for the assessment of needs of the various raions in the oblast based on the recent reports of cases and estimates of future cases. The Raion Unit is responsible for drug supply to the different facilities operating in the raion and to health workers supervising the patient's continuation phase of treatment.

A comprehensive management plan for the pharmacy for maintaining accurate inventory, for dispensing drugs to inpatients, for distributing drugs to the raions and prison system, for calculating drug supply needs, and for requesting new drug supplies should be developed by the Central Unit for use by the oblasts.

C. Evaluation

1. Recording and Reporting System

A recording and reporting system using standardised forms will be established. This system provides clear information on disease classification and case category and, through cohort analysis, information on treatment results. The examples of forms are included in Annex 5.

1a. **Tuberculosis Register:(TB03)** The main TB register is maintained and updated at the oblast TB program level and individual raion registers are kept by the Raion Co-ordinator. The register contains: date of registration, serial number, name, sex and age, address, disease classification, case category, date of start of treatment, prescribed regimen, space for recording dates, lab number, and results of smear, culture, and drug susceptibility examinations of patients with pulmonary tuberculosis and results of treatment, i.e., cured, treatment completed, died, failure, interrupted, transferred out.

1b. **Tuberculosis Treatment Card:(TB01)** Every patient registered in the raion tuberculosis register has a tuberculosis treatment card. The card contains details on treatment, regimen, and drug dosages. The treatment card is introduced at the dispensary where the initial phase of treatment is administered. After the initial phase has been completed, the treatment card is sent to the outpatient facility where the continuation phase of treatment is to be administered. A copy of the treatment card is sent to the Raion Co-ordinator. The Raion Co-ordinator is responsible to ensure that the relevant data from the treatment card are transferred to the raion tuberculosis register. In cities with an oblast dispensary, patients diagnosed and treated within that facility are registered in the same type of register as the one in use at the raion level.

1c. **Patient Identity Card: (TB 02).** Each patient is provided with a standard patient identity card which is kept by the patient upon discharge from the raion or oblast dispensary. It contains relevant information on patient treatment and space for appointment dates for the continuation phase.

1d. **Tuberculosis Laboratory Register: (TB 04).** This is kept in all laboratories performing smear microscopy. It contains a unique lab number for a patient, relevant personal data on the patient, reason for smear test (diagnosis or treatment monitoring), smear test results, and a column for remarks. The Raion Co-ordinator is responsible to check whether all patients with positive smear in the laboratory registers were entered in the raion tuberculosis register. Each laboratory will be responsible for following up and recording smear and culture results of specimens collected.

1e. **Sputum Collection Book:** All peripheral health staff (primary health care doctors and feldshers) should be instructed on collection of sputa from patients suspected to have tuberculosis. Sputa of these patients should be sent to the designated laboratory for testing. The health care worker should record the name and address of the patient, reason for smear test, and date of sputum collection and dispatching in a sputum collection book. This will allow rapid tracing of patients who do not return for the required diagnostic tests.

Reports on case finding and treatment results will be sent from the raions to the Oblast Unit for monitoring DOTS activities, identification of problems, and evaluating results. The Oblast Unit will send the reports to the Central Unit which is responsible for assessing them and sending them to CDC, WHO, and USAID.

The four forms are:
1. Quarterly Report on New Cases and Relapses of tuberculosis: (TB 07)
2. Quarterly Report on Sputum Conversion: (TB 10)
3. Quarterly Report on Treatment Results of Smear-positive Pulmonary Tuberculosis Patients Registered 12-15 Months Earlier: (TB 08)
4. Quarterly Report on Laboratory Activities

These forms will be completed by the Raion Co-ordinator, sent in due time (the report of new cases and relapses should reach the Oblast Unit within 14 days of the beginning of a following quarter), collected and checked by the Project Supervisor who submits them to the Oblast Data Unit for computerization. The forms contain information on diagnosed cases of tuberculosis (new and other cases) in a cohort of patients who were entered in the raion tuberculosis register during a three-month period and on smear conversion and treatment results in the same cohort.

It is the responsibility of staff at the Oblast Unit to calculate the indicators that are described below and to include them in the report to the Central Unit. The Central Unit will provide these to CDC, USAID, and WHO. The Central Unit has ultimate responsibility for supervising the evaluation of performance of the DOTS projects.

2. Indicators evaluating effectiveness of the DOTS projects

2a. Laboratory Performance Indicators

1) Positivity rate smear microscopy among suspects:
   Number of smear positive patients out of all suspect cases examined
2) Positivity rate smear microscopy among follow-up patients:
   Number of smear positive patients out of all follow-up patients
3) Percentage of cultures succeeded:
   Number of cultures with and without growth out of all cultures done
4) Positivity rate of cultures:
   Number of positive cultures out of all cultures done
5) Positivity rate and negativity rate of cultures from smear-positive sputum samples
6) Positivity rate and negativity rate of cultures from smear negative sputum samples
7) Quarterly report on drug susceptibility testing

2b. Case-finding Indicators

1) Absolute numbers of all newly notified cases (new and relapses) by disease classification and:
   - Proportion of pulmonary smear-positive out of all newly notified cases
   - Proportion of pulmonary smear-negative out of all newly notified cases
   - Proportion of extra-pulmonary cases out of all newly notified cases

2) Absolute number of newly notified cases by type of disease:
   - New cases
   - Relapses
   - Age and sex specific breakdown of all newly notified smear-positive cases

3) Incidence rate of pulmonary smear-positive tuberculosis cases, i.e., new pulmonary smear-positive cases notified during a given year per 100,000 population (based on the official population estimate for the year studied).

2c. Treatment Result Indicators

1) Smear conversion rate: Number of new smear-positive cases who were negative at the end of the initial phase of treatment out of all new smear-positive cases registered in the respective cohort analysis quarter.

2) Cure Rate: Number of new sputum smear and/or culture-positive cases who completed treatment and had at least two negative sputum smear and culture results one of which was at completion of treatment out of the total number of new smear-positive cases registered for treatment.

3) Treatment Completion Rate: Number of new sputum smear (culture)-positive cases who completed treatment with negative smears and cultures at the end of the initial phase but with no or only one negative sputum examination in the continuation phase and none at the end of treatment out of the total number of new smear-positive cases registered for treatment.

4) Death Rate: Number of new sputum smear-positive cases who died during treatment regardless of cause out of the total number of new smear-positive cases registered for treatment.

5) Failure Rate: Number of new sputum smear (culture)-positive cases (on sputum microscopy and culture) who remained or became again smear (culture)-positive at five months or later during treatment out of the total number of new smear (culture)-positive cases registered for treatment.

6) Interruption Rate: Number of new sputum smear-positive cases who interrupted treatment for two months or more (2 or more weeks – for those treated over 2 months) out of the total number of new smear-positive cases registered for treatment.

7) Transferred Out Rate: Number of new sputum smear (culture)-positive cases who moved to to another raion or oblast or were transferred under another jurisdiction during the course of treatment and whose treatment results are not known out of the total number of new smear-positive cases registered for treatment.

The same system should be used to evaluate results of new smear (culture)-negative cases, re-treatment and other cases.
Additional estimation is made of:

Treatment success indicator:
For new cases:
Number of the newly-diagnosed smear/culture-positive and smear/culture-negative patients with tuberculosis whose treatment outcome was interpreted as "cured" or "treatment completed" out of the total number of new cases registered for treatment.

The same procedure is followed for estimating the treatment success indicator for re-treatment and other cases.

2d. Program Management Indicators

1) Implementation of supervisory visits plan: Number of supervisory visits conducted per level compared to number to be expected per level

2) Proportion of quarterly reports properly completed and received: The number of reports properly completed compared to a total number of reports

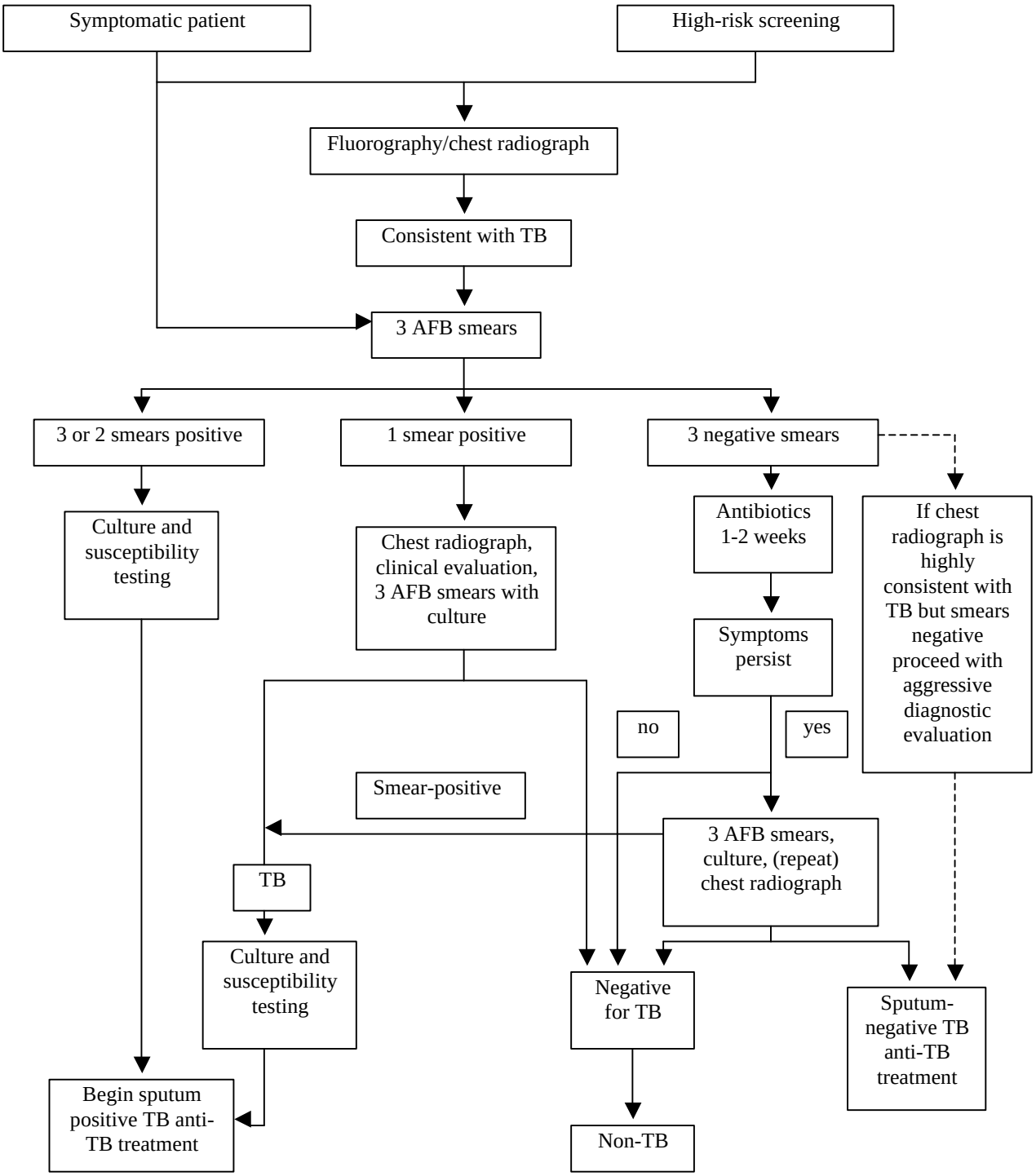
3) Consumption of drugs and supplies used in a quarter: Total number of drugs and supplies used in a quarter compared with the estimated number

4) Proportion of slides accurately read as smear-positive or smear-negative: The number of slides accurately read compared with the entire sample of slides sent for quality control

3. Reporting

Regular reporting to CDC, WHO, and USAID should be done by the Central Unit on a quarterly basis.

Annex 1. Diagnosis of Pulmonary Tuberculosis



Annex 2a. Treatment schedules and doses, Category I and Category III Patients

Intensive Phase, dosing daily for 2-3 months

	Adults		Children	
	Dose (mg/kg)	Maximum daily dose (mg)	Dose (mg/kg)	Maximum daily dose (mg)
Isoniazid	5	400	5	300
Rifampin	10	600	10	600
Pyrazinamide[1]	25	2000	25	2000
Ethambutol[2,3]	20	-	15	-
Streptomycin[4]	15	1000	20	1000

[1] For weight < 50kg or age > 60 years, use 1500mg

[2] No ethambutol for children < 6 years

[3] For patients with renal insufficiency, the ethambutol dosing interval should be increased to every 36 hours for those with 50-75% reduction in creatinine clearance and to 48 hours for those with >75% reduction in creatinine clearance.

[4] For weight < 50kg or age > 60 years, use 750mg

Continuation Phase, dosing three days per week for 4-6 months

	Adults		Children	
	Dose (mg/kg)	Maximum daily dose (mg)	Dose (mg/kg)	Maximum daily dose (mg)
Isoniazid	10	900	10	900
Rifampin	10	600	10	600
Pyrazinamide	35	3000	35	3000
Ethambutol[1]	30	-	30	1000
Streptomycin	25	1500	25	1500

[1] No ethambutol for children < 6 years

Annex 2b. Treatment schedules and doses, Category II Patients

Intensive Phase, dosing daily for 3 months

	Adults		Children	
	Dose (mg/kg)	Maximum daily dose (mg)	Dose (mg/kg)	Maximum daily dose (mg)
Isoniazid	5	400	5	300
Rifampin	10	600	10	600
Pyrazinamide[1]	25	2000	25	2000
Ethambutol[2-3]	20	-	15	-
Capreomycin	15	-	15	-
Ofloxacin[4]	15	-	Do not use in children	
Ethionamide	10	-	10	-

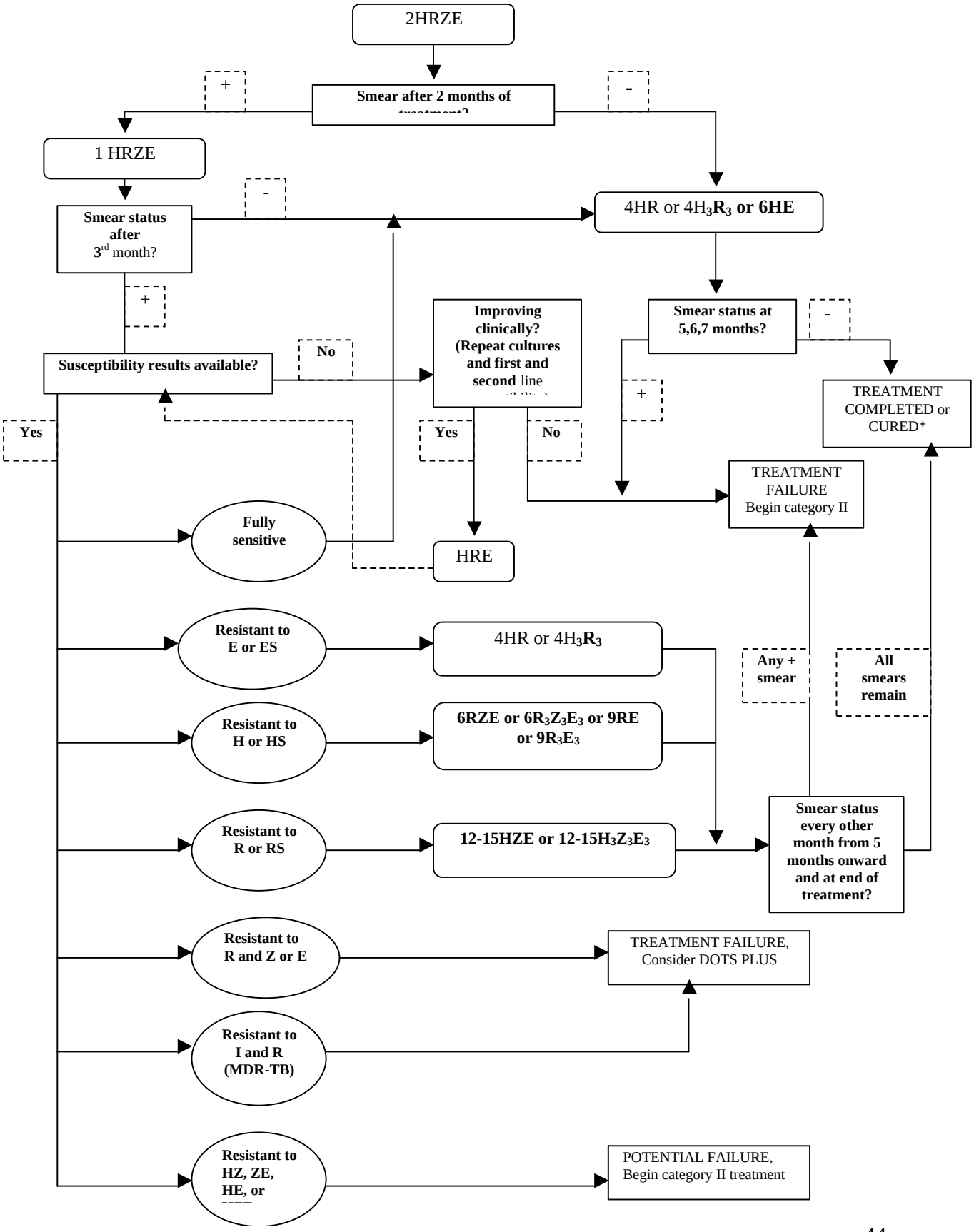
[1] For weight < 50kg or age > 60 years, use 1500mg
[2] No ethambutol for children < 6 years
[3] For patients with renal insufficiency, the ethambutol dosing interval should be increased to every 36 hours for those with 50-75% reduction in creatinine clearance and to 48 hours for those with >75% reduction in creatinine clearance.
[4] For weight < 50kg or age > 60 years, use 750mg; no ofloxacin for children

Continuation Phase, dosing three days per week for 5 months

	Adults		Children	
	Dose (mg/kg)	Maximum daily dose (mg)	Dose (mg/kg)	Maximum daily dose (mg)
Isoniazid	10	900	10	900
Rifampin	10	600	10	600
Pyrazinamide	35	3000	35	3000
Ethambutol	30	-	30	1000
Capreomycin	15	-	15	1500
Ofloxacin	15	-	Do not use in children	
Ethionamide[1]	-	-	-	-

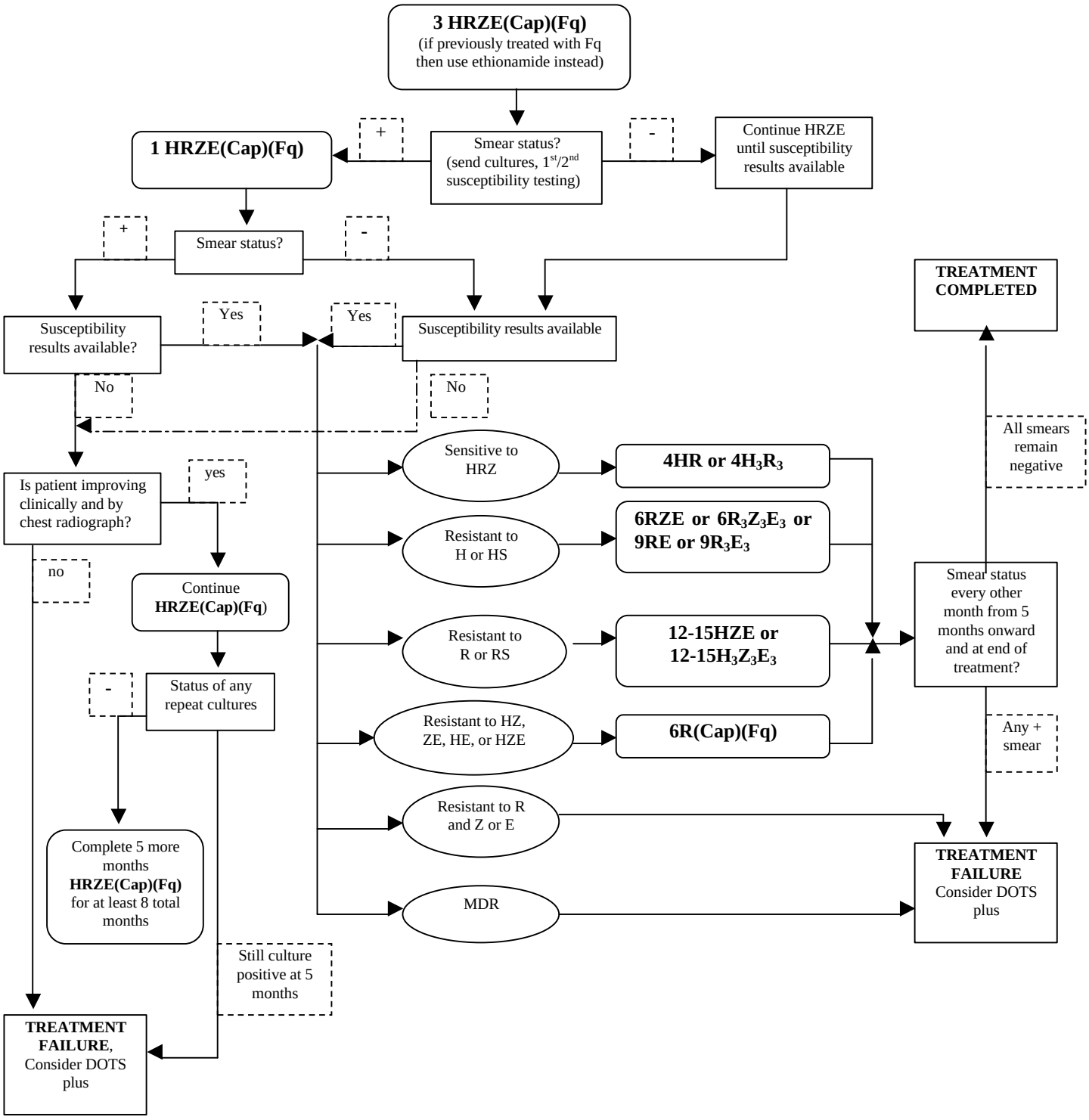
[1]No data available for dosing ethionamide three days per week

Annex 3a. Category I Treatment Algorithm

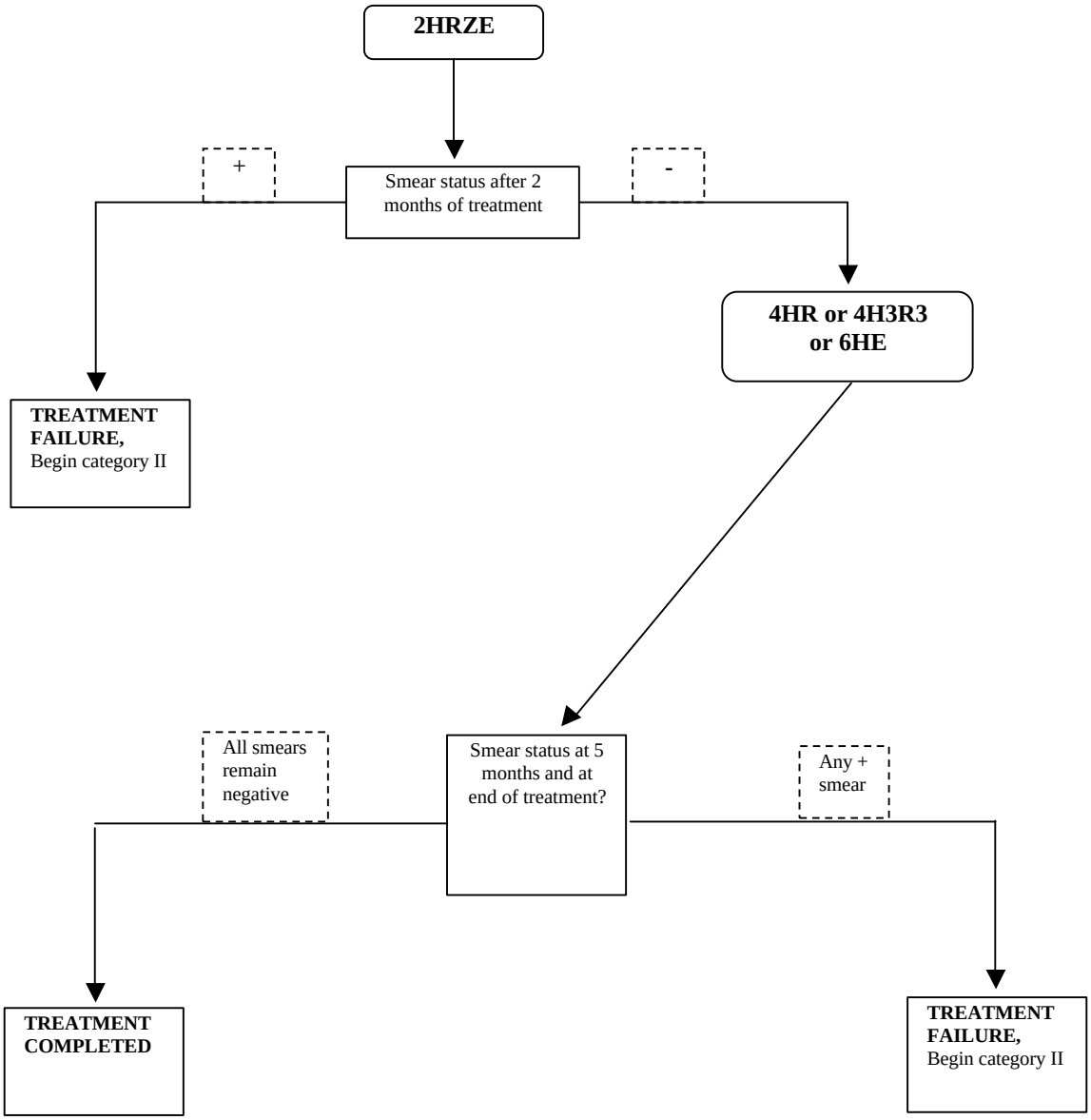


* If patient is sputum smear negative but culture positive at 5 month or later: treatment failure

Annex 3b. Category II Treatment Algorithm



Annex 3c. Category III Treatment Algorithm



Annex 4a. Management of Patients Who Interrupt Treatment, Category I

Treatment received before interruption	Length of interruption	Perform a sputum analysis	Result of sputum smear analysis	Outcome	Re-registration	Treatment
Less than 1 month	Less than 2 weeks	No	-	-	-	Continue Cat I*
	2-7 weeks	No	-	-	-	Start again on Cat I**
	8 weeks or more	Yes	Positive	Default	Treatment after interruption	Start again on Cat I**
			Negative	-	-	Continue Cat I*
1-2 months	Less than 2 weeks	No	-	-	-	Continue Cat I*
	2-7 weeks	Yes	Positive	-	-	1 extra month of intensive phase of cat I
			Negative	-	-	Continue cat I*
	8 weeks or more	Yes	Positive	Positive	Treatment after interruption	Start on cat II**
			Negative	-	-	Continue cat I*
More than 2 months	Less than 2 weeks	No	-	-	-	Continue cat I*
	2 weeks or more	Yes	Positive	Default	Treatment after interruption	Start on cat II**
			Negative	-	-	Continue cat I*

* A patient must complete all 60 doses of the initial intensive phase.
** A patient who must restart treatment from the beginning

Annex 4b. Management of Patients Who Interrupt Treatment, Category II

Treatment received before interruption	Length of interruption	Perform a sputum analysis	Result of sputum smear analysis	Outcome	Re-registration	Treatment
Less than 1 month	Less than 2 weeks	No	-	-	-	Continue Cat II*
	2-7 weeks	No	-	-	-	Start again on Cat II**
	8 weeks or more	Yes	Positive	Default	Treatment after interruption	Start again on Cat II**
			Negative	-	-	Continue Cat II*
1-2 months	Less than 2 weeks	No	-	-	-	Continue Cat II*
	2-7 weeks	Yes	Positive	-	-	1 extra month of intensive phase of cat II
			Negative	-	-	Continue cat II*
	8 weeks or more	Yes	Positive	Positive	Treatment after interruption	Start again on cat II**
			Negative	-	-	Continue cat II*
More than 2 months	Less than 2 weeks	No	-	-	-	Continue cat II*
	2 weeks or more	Yes	Positive	Default	Treatment after interruption	Start again on cat II**
			Negative	-	-	Continue cat II*

* A patient must complete all 90 doses of the initial phase

** Although this patient does not strictly fit the definition of default, default most closely describes the outcome of this patient, although at re-registration they should be categorized as "other"

Annex 4c. Management of Patients Who Interrupt Treatment, Category III

Treatment received before interruption	**Length of interruption**	**Do a sputum examination**	**Result of sputum smear examination**	**Outcome**	**Re-registration**	**Treatment**
Less than 1 month	Less than 2 months	No	-	-	-	Resume treatment and complete all doses
	2 months or more	Yes	Positive	Default	Treatment after interruption	Begin cat III afresh
			Negative	-	-	Resume treatment and complete all doses
More than 1 month	Less than 2 months	No	-	-	-	Resume treatment and complete all doses
	More than 2 months	Yes	Positive	Default	Treatment after interruption	Begin cat II treatment afresh
			Negative	-	-	Resume treatment and complete all doses

Annex 5. Recording and Reporting Form

Available in the WHO Training Modules: “Managing tuberculosis at the district level”

Annex 6. Collaborative Partners and Responsibilities in the TB control Projects in Ivanovo, Orel and Vladimir

- Oblast TB Dispensaries

- Central TB Research Insitute, Russian Academy of Medical Science, Moscow

    - Dr Punga V.V. ; Director Ivanovo TB Control Program
    - Dr Vassilieva I.A. ; clinical curator Ivanovo TB Control Program
    - Dr Puzanov V.A.; bacteriological curator Ivanovo and Vladimir Program
    - Dr Ribka L.N. ; administrative and clinical curator Orel TB Control Program
    - Dr Shulgina M.V. ; bacteriological curator Orel TB Control Program
    - Dr Putova E.V. ; administrative and clinical curator Vladimir TB Control Program

- World Health Organization (WHO), Office of the Special Representative of the Director-General, Moscow

    - Dr Wieslaw Jakubowiak, TB Coordinator
    - Dr Hans Kluge, TB Project Manager

- U.S. Centers for Disease Control and Prevention (CDC), Atlanta, Georgia

    - Dr Peter Cegielski, Advisor Ivanovo TB Control Program
    - Dr Charles Wells, Advisor Orel TB Control Program
    - Mr Gustavo Aquino, Public Health Advisor for Ivanovo, Orel and Vladimir

- U.S. Agency for International development (USAID), Moscow

    - Mr George Oswald
    - Dr Nikita Afanasiev

WHO is the ultimate project coordinator.WHO has the final decision on procurement and supply issues.
The overall project management is the joint responsibility of WHO and CTRI.
CDC is the technical advisor for the TB control projects, working under the umbrella of WHO.
USAID is the donor of the WHO supported projects in Ivanovo, Orel and Vladimir.